Evaluation of amlodipine, lisinopril, and a combination in the treatment of essential hypertension

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Abstract
Angiotensin converting enzyme (ACE) inhibitors and dihydropyridine calcium antagonists are well established and widely used as monotherapy in patients with mild to moderate essential hypertension. Earlier studies combining short acting drugs from these classes require multiple dosing and were associated with poor compliance. Availability of longer acting compounds allows once daily administration to avoid the inconvenience of a multiple daily dose. It was decided to perform a randomised double blind, crossover study with the long acting calcium channel blocker amlodipine and the long acting ACE inhibitor lisinopril, given either alone or in combination in essential hypertension. Twenty four patients with diastolic blood pressure (DBP) between 95 and 104 mm Hg received amlodipine 2.5 mg and 5 mg, lisinopril 5 mg and 10 mg, and their combination as per a prior randomisation schedule. Supine and standing blood pressure and heart rate were recorded at weekly intervals. Higher doses of both the drugs individually or in combination were used if the target supine DBP below 90 mm Hg was not achieved. There was a significant additional blood pressure lowering effect with the combination when compared either with amlodipine or lisinopril alone. Five mg amlodipine and 10 mg lisinopril monotherapy achieved the target blood pressure in 71% and 72% patients respectively. The combination of 2.5 mg amlodipine with 5 mg lisinopril produced a much more significant lowering of blood pressure in a higher percentage of patients than that with an individual low dose.
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Keywords: amlodipine; lisinopril; hypertension; combination therapy

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It is well known that monotherapy does not provide therapeutic response in all hypertensives. Some patients show an excellent response, while in others there is a poor response. Combination antihypertensive therapy is administered when blood pressure is inadequately controlled by monotherapy to achieve a balanced and additive antihypertensive effect with minimum adverse effects.[1] Until recently, combination therapy generally employed a diuretic, but the availability of new classes of drugs and improved agents within the existing classes now provides a multitude of potential drug combinations.[1] Proper understanding of the underlying mechanism by which the various classes of antihypertensive drugs act together provides the rationale of developing effective combinations.[2]

Both angiotensin converting enzyme (ACE) inhibitors and dihydropyridine calcium antagonists are well established and widely used in monotherapy. An understanding of differences in the mechanism of action of these agents allows a logical approach for the use of these agents as a combination therapy. Calcium antagonists are vasodilatory and tend to increase plasma renin, therefore combination with an ACE inhibitor is theoretically sound.[3] Furthermore, calcium antagonists of the dihydropyridine group have been shown to have a diuretic and natriuretic effect, which again should combine well with ACE inhibitors.[4] Calcium antagonists and ACE inhibitors in combination reduce blood pressure more than either drug alone.[4]

Regardless of the order of administration, the combination of nifedipine and captopril was found to be significantly more effective than the individual agents.[5] However the effect was short lived due to the short duration of action of both the drugs. Therapy with 5 mg enalapril and 5 mg felodipine produced a significant decrease in both supine and erect blood pressure.[6] Longer acting compounds of both classes, like amlodipine and lisinopril, have now become available allowing once daily administration.

The aim of the present study was to compare in a double blind, randomised, crossover design, the efficacy and safety of the long acting calcium channel antagonist amlodipine and the long acting ACE inhibitor lisinopril, individually and in combination in mild to moderate hypertension.

Patients and methods

Patients presenting to the outpatient department with mild to moderate hypertension, with a supine diastolic blood pressure (DBP) between 95 and 104 mm Hg, after two weeks off all antihypertensive treatment, and found to have no secondary cause of hypertension, were enrolled. Patients with renal and hepatic impairment, ischaemic heart disease, cerebrovascular disease, diabetes mellitus, pregnant women, or those who were taking oral contraceptives were excluded from the study. Before inclusion into the present study protocol, regular measurement of blood pressure was carried out at weekly intervals for four weeks. Patients

Table 1   Effect of amlodipine, lisinopril, and their combination on mean blood pressure and heart rate; values are mean (SD)

	Supine			Standing		
	SBP (mm Hg)	DBP (mm Hg)	Heart rate (bpm)	SBP (mm Hg)	DBP (mm Hg)	Heart rate (bpm)
Placebo	149 (10)	98 (6)	76 (6)	155 (11)	103 (7)	77 (8)
Amlodipine 2.5 mg	140 (11)★	92 (7)★	73 (6)	143 (12)★	93 (8)★	76 (5)
Amlodipine 5 mg	137 (7)★	85 (6)★	74 (5)	138 (6)★	88 (6)★	76 (7)
Lisinopril 5 mg	138 (10)★	90 (8)★	75 (5)	140 (10)★	92 (6)★	76 (4)
Lisinopril 10 mg	136 (9)★	87 (5)★	74 (3)	138 (9)★	98 (5)★	77 (5)
Amlodipine 2.5 mg + lisinopril 5 mg	131 (9)★	82 (7)★	73 (5)	132 (9)★	83 (7)★	74 (4)
Amlodipine 5 mg + lisinopril 10 mg	127 (9)★	79 (5)★	74 (5)	129 (7)★	79 (5)★	77 (4)

DBP = diastolic blood presssure; SBP = systolic blood pressure.
★p<0.001.

gave their written informed consent for their participation in this institutional ethics committee approved study. A total of 30 patients (16 male and 14 female) fulfilled the inclusion and exclusion criteria and were included in the study.

After four weeks of a placebo run in phase, patients entered in the double blind, randomised crossover study phase. Patients were randomised to receive initially amlodipine or lisinopril and then their combination. Each active drug treatment period lasted for four weeks. In monotherapy, amlodipine was used in the dose of 2.5 mg daily for two weeks, the dose was increased to 5 mg daily for patients in whom the supine DBP was above 90 mm Hg. The other group received lisinopril 5 mg daily for two weeks, then increased to 10 mg daily if supine DBP was more than 90 mm Hg. For combination therapy, treatment was started with 2.5 mg amlodipine and 10 mg lisinopril per day. If after two weeks, the supine DBP was more than 90 mm Hg, a combination of 5 mg amlodipine and 10 mg lisinopril was used. Blood pressure was measured at each visit between 9 am and 10 am, 24 hours after the previous dose.

The supine (10 min) and standing (2 min) blood pressure were determined with appropriate cuff size by the same observer using L&T Minimon 7133 A blood pressure monitor and the mean of three readings was noted. Pulse rate was recorded simultaneously using a L&T Micromon 7142 pulse monitor. Patients were asked if there had been any change in their presenting symptoms or development of new symptoms at each follow up visit.

Patients were instructed to return unused medications at each follow up visit to know the compliance. Antihypertensive efficacy between the treatment schedules was compared using analysis of variance and the paired *t* test.

Results

Patients who received even a single dose of active treatment were included in this intent-to-treat analysis to compare the effect of various phases of treatment phases. A total of 30 patients (16 males and 14 females), mean (SD) age 49.8 (9.0) years (range 41–62 years), were enrolled. Out of the 30 patients enrolled, 24 completed all the phases of the study. Six patients were lost to follow up. Mean supine and standing blood pressure and heart rate at the end of each treatment phase are shown in

table 1. After the placebo run in phase, the mean (SD) supine blood pressure was 149 (10)/98 (6) mm Hg and the standing blood pressure was 155 (11)/103 (7) mm Hg. The supine and standing heart rate were 76 (6) and 77 (8) beats/min respectively. Amlodipine 2.5 mg and 5 mg produced a significant fall in both supine and standing blood pressure. Treatment with lisinopril in doses of 5 mg and 10 mg also significantly decreased supine and standing blood pressure. The mean DBP (below target 90 mm Hg) was achieved in a higher percentage of patients with 5 mg amlodipine and 10 mg lisinopril monotherapy. There was a greater reduction in systolic blood pressure (SBP) and DBP in supine and standing positions with the combination of amlodipine and lisinopril than the individual drugs. Combination of amlodipine 2.5 mg and lisinopril 5 mg reduced the mean DBP below 90 mm Hg in 54% of patients.

The mean (SD) supine blood pressure was significantly reduced from 149 (10)/98 (6) to 140 (11)/92 (7) and 137 (7)/85 (6) mm Hg with 2.5 and 5 mg amlodipine respectively (p<0.001). There was a significant fall in standing blood pressure from 155 (11)/103 (7) to 143 (12)/93 (8) and 138 (6)/88 (6) mm Hg with 2.5 and 5 mg amlodipine respectively (p<0.001).

Lisinopril at 5 mg and 10 mg also produced a significant dose dependent decrease in supine and standing blood pressure from the basal value to 138 (10)/90 (8), 136 (7)/87 (5), 40 (10)/92 (6), and 138 (9)/89 (5) mm Hg respectively (p<0.001). There was a more marked fall in blood pressure with the combination of amlodipine and lisinopril than with either drug given individually. Amlodipine 2.5 mg with 5 mg lisinopril lowered supine and standing blood pressure to 131 (9)/82 (7) and 132 (9)/83 (7) mm Hg respectively (p<0.001). Amlodipine at 5 mg plus lisinopril at 10 mg in combination produced a more significant fall in supine and standing blood pressure to 127 (9)/ 79 (5) and 129 (7)/79 (5) mm Hg respectively. The target standing DBP below 90 mm Hg could be achieved in 29%, 71%, 25%, and 72% patients with amlodipine 2.5, 5 mg and lisinopril 5 mg, 10 mg dose respectively. DBP below 90 mm Hg could be achieved in 54% and 100% patients with a combination of amlodipine 2.5 plus lisinopril 5 mg and amlodipine 5 mg plus lisinopril 10 mg respectively (fig 1). None of the treatment regimens
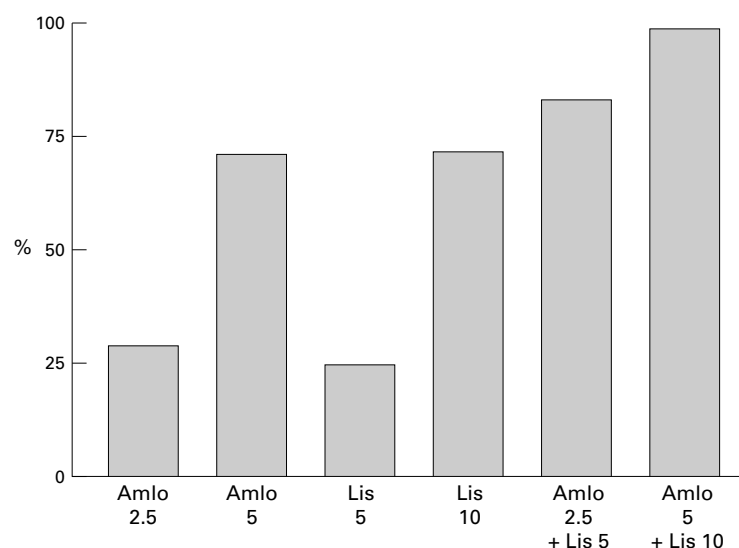
Figure 1   Percentage of patients who achieved target blood pressure (DBP below 90 mm Hg). Amlo 2.5 = amlodipine 2.5 mg; Amlo 5 = amlodipine 5 mg; Lis 5 = lisinopril 5 mg; Lis 10 = lisinopril 10 mg; Amlo 2.5 + Lis 5 = amlodipine 2.5 mg + lisinopril 5 mg; Amlo 5 + Lis 10 = amlodipine 5 + lisinopril 10 mg.

Table 2   Number of patients complaining of side effects

Side effects	Placebo	Amlodipine		Lisinopril		Combination	
		2.5 mg	5 mg	5 mg	10 mg	2.5+5	5+10
Headache	3	4	4	0	0	2	3
Ankle oedema	0	1	4	0	0	0	0
Dizziness	1	0	0	1	2	0	2
Throat irritation	0	0	0	3	2	1	1
Drowsiness	1	1	2	0	2	0	2
Cough	0	0	0	3	2	0	0
Palpitation	0	0	1	0	0	0	0
Nausea	1	1	2	0	1	0	1
Total	6	7	13	7	9	3	8

produced any significant change in mean heart rate. All patients tolerated the treatment schedules well without any serious side effects.

The frequency of side effects observed with each treatment is shown in table 2. Ankle oedema was more frequent with amlodipine, while throat irritation and cough was reported with lisinopril. These particular side effects were seen more in monotherapy and were much less frequent during combination therapy.

Discussion

Many antihypertensive agents are available in the market. Any of these drugs when used alone as a monotherapy are effective in only 40%–60% of patients with hypertension.[7] Several studies reported that combination treatment using antihypertensive agents of two different classes are useful and promising in controlling blood pressure in patients with hypertension.[8 9] Calcium channel blockers and ACE inhibitors in combination reduce blood pressure more than either drug alone.[5] In the present study we observed more effective lowering of blood pressure to the target value with amlodipine and lisinopril in combination. Singer *et al* demonstrated a greater blood pressure lowering effect when nifedipine and captopril were combined.[5] However, they found the effect of the combination to be short

lasting. Similar observations were also made in a small group of patients who were on a captopril and nifedipine combination.[10]

Although the combination was more effective than monotherapy in lowering blood pressure, frequent dosing was required for adequate blood pressure control.[11] In the present study, the combination of long acting drugs of the two classes, namely amlodipine and lisinopril, reduced blood pressure more than either drug alone even 24 hours after dosing. This clearly shows that the combination has a marked additional and long lasting effect on blood pressure.

In the present study, at the end of lisinopril treatment phase, 72% of patients achieved a fall in DBP to the target value and with amlodipine it could be achieved in 71% of patients.

Combination of the two drugs, irrespective of their order, reduced blood pressure to the target value in 100% of patients. Perhaps the most efficient and conceptually attractive approach in the treatment of patients in whom ACE inhibitor or calcium channel blocker monotherapy fails, is to combine the two agents, thereby blocking the major vasoconstrictive mechanisms.[12] The efficacy of a calcium channel blocker is enhanced by concomitant use of an ACE inhibitor, methyldopa, or β-blocker.[13]

Ninety per cent of patients with mild to moderate hypertension are controlled by combination of an ACE inhibitor with either a calcium channel blocker, α-adrenergic receptor blocker, or diuretic.[14]

Isolated systolic hypertension is a definite risk factor for cardiovascular morbidity and mortality independent of diastolic elevation. These complications include coronary artery disease, stroke, and cardiac failure.[15] Raised SBP leads to an increase in myocardial oxygen consumption with an enhanced rise of an acute coronary event, lowering of SBP, and thus might be advantageous especially in hypertensives with ischaemic heart disease.[16] In the present study, lowering of SBP with a combination of amlodipine and lisinopril will be beneficial. In a double blind placebo controlled study, 2 mg and 4 mg of a new calcium antagonist, lacidipine, were shown to cause significant reduction in SBP variability and provided adequate control of arterial hypertension.[17] The mechanism of additive effect of these two classes of drugs used in the present study is not clear. Dihydropyridines such as nifedipine cause acute natriuresis and diuresis[18] resulting in long lasting loss of sodium and water.[19] This effect is also likely to be present with amlodipine.[20] Loss of sodium and water leads to activation of the renin angiotensin-aldosterone system, after treatment with dihydropyridine calcium antagonists, reflecting an increase in circulating concentrations of angiotension II. These effects are likely to offset partly the blood pressure lowering effect of dihydropyridines.[20] Addition of an ACE inhibitor blocks the rise in angiotensin II activity and thus potentiates the effect of calcium channel blockers on blood pressure. ACE inhibitors

may also potentiate the action of dihydropyridines by buffering the baroreflex mediated increase in heart rate secondary to vasodilatation due to calcium channel blockers or by indirectly inhibiting the sympathetic nervous system.[1] Amlodipine and lisinopril monotherapy produced a similar fall in blood pressure in our study but a greater blood pressure lowering effect was noticed with the combination of the two drugs. Morgan and Anderson reported a higher blood pressure lowering effect with the combination of low doses of enalapril and felodipine.[6]

Short acting dihydropyridines are known to produce reflex tachycardia. In the present study, amlodipine monotherapy did not produce any tachycardia, particularly in a standing position. The ACE inhibitor captopril, in combination, effectively blocked nifedipine induced tachycardia.[10] We did not find any significant change in heart rate, suggesting that there is no significant stimulation of the sympathetic nervous system during amlodipine therapy. Cappuccio *et al* also reported similar results with 5 mg amlodipine in their study.[20]

One advantage of combination therapy is that there is an additive effect on blood pressure so that lower doses of both drugs can be given, mitigating side effects. We found that the incidence both of oedema of the feet and cough was less during combination therapy than with either drug alone. Recently, a combination product containing amlodipine and benazapril has been approved for clinical use. This combination was found to be more effective than individual monotherapy with significantly lower overall side effects, particularly headache and oedema.[21] In a dose response relationship study, enalapril and felodipine were given alone and in combination in 707 patients and the combination was associated with less peripheral oedema than felodipine alone.[22] Similarly, ankle oedema associated with nifedipine therapy disappeared in three of four patients after the addition of captopril.[23 24] In another study, the incidence of swollen ankle was significantly more with felodipine monotherapy compared with a combination of felodipine and enalapril.[6]

The combination of ACE inhibitors with calcium channel blockers may provide other special values.[25] There is evidence that reflex tachycardia associated with the dihydropyridine group is corrected by a parasympathetic influence[26 27] and that of peripheral oedema is corrected by the postcapillary or venodilating effect of added converting enzyme inhibitor.[24]

The large majority of currently marketed preparations contain a thiazide diuretic or a β-blocker with a calcium channel blocker. Results of studies with more novel combinations such as ACE inhibitors and calcium channel blockers will provide a regimen that is more effective with minimum side effects.

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